Nicotine Safety

Selected Animal Data

Few animal studies have looked at the effects of chronic or lifelong exposure to nicotine alone. However I would like to bring to the committee's attention the study by Waldum (1) where generally no harmful effects on any organs could be detected after rats were exposed to inhaled nicotine for two years, almost their entire life. A particular concern about nicotine safety is its effects on the foetus. From Slotkins and co-workers studies it seems undisputed that nicotine alone can have a negative effect particularly on the development on the foetus' cholinergic nervous system. I will briefly return to the discussion of nicotine use during pregnancy in my conclusion.

Human Data

Over the last twenty years our understanding of the effects of nicotine has improved gradually. Still however many, even physicians, believe that nicotine is causing e.g. cancer and other diseases. There seem to be little reason to believe nicotine is causing cancer or respiratory diseases. On the cardiovascular system the case is less clear and therefore a good number of studies have addressed the effects on cardiovascular risk factors and disease. Neal Benowitz has continuously reviewed this area and the current prevailing judgement seem to be that there is little reason to believe that nicotine, at least as delivered by current nicotine replacement products, is associated with an increased risk of cardiovascular disease. Some important studies here are the safety data from long-term nicotine gum chewers from the American Lung Health Study (2) where no detrimental effects of long-term (five years) gum use could be detected. On cardiovascular disease (number of hospitalisations due to cardiovascular disease) there was if anything a protective effect of long-term nicotine use. More recently the relationship between myocardial infarction and the use of nicotine patch has been investigated in a large case control study (3). No relation was found and again if anything the patch seem to have a protective effect for heavy smokers.

The Effects of Nicotine as Studied by the Swedish Snus

The association of snus – the Swedish form of smokeless tobacco – and diseases is of importance for two reasons. First, because snus delivers similar amounts of nicotine as cigarettes but does not deliver carbon monoxide and other gases and delivers very few carcinogens. Thus, if nicotine itself is part of the cause of increased cardiovascular disease in smokers, one would expect snus users to also have higher rates of cardiovascular disease. If non-nicotine substances are the causes of the increased CV disease, then there should be no increase in CV disease in snus users. Second, some scientists and clinicians have suggested that smokers who cannot stop smoking should switch to snus as a less-risky alternative.

Snus is a smokeless tobacco product with very fine cut tobacco, powder like, that is moist and the nicotine content is about 1%. The snus which is usually packed in small saches is put between the upper lip and gum. Snus appears to have less tobacco specific nitrosamines than many other smokeless tobacco products. Snus is not fermented, as commonly is the case with smokeless tobacco products. In the end of the manufacturing process, before packaging, the tobacco is more or less sterilised by exposing the tobacco to hot water vapour. After packaging the product

is kept cool, even in the final outlet, which might help keep the product stable and avoid growth of bacteria and formation of nitrosamines.

The use of snus among men is a long standing tradition in the Swedish society. It was very common in the early decades of the last century. It faded out when the cigarette became popular after the Second World War but during the last 20-30 years has gained in popularity again. Today 19% of Swedish adult men use snus daily and 16% smoke cigarettes. Of females there is less then 1% that are daily snus users. In physicians 9% are using snus and 6% smoke.

Acute Studies on Cardiovascular Risk Parameters

There are mainly two groups that have looked at the effects of snus on the heamodynamic, atherogenic and metabolic variables, Eliasson and Bolinder. A number of these studies are enclosed (4-7). The results from these studies have certainly shown that there is a large difference in the effect of cigarette smoking and snus. The risk profile of snus users is more benign and the effects of acute administrations are less pronounced with snus. In many instances it is hard to detect any differences between snus and a no nicotine condition.

Snus Use and Cardiovascular Disease

There are three published epidemiological studies on the relationship between tobacco use (smoking and snus) and their association with mainly myocardial infarction. Huhtasaari (8) found in a case (n=585) control (n=589) study as part of the WHO Monica project in men 35-64 years old who had their first MI that the adjusted OR for current snus use was 0.89 (CI 0.62-1.29) and 1.87 (CI 1.40-2.48) for smoking compared with non tobacco users. Low snus consumers, less than 2 cans a week, had a significant lower infarction incidence (OR 0.63, CI 0.41-0.98).

Huhtasaari (9) again, as part of the WHO Monica project, looked at first MI in men 25-64 years old in 687 cases and 687 controls. The unadjusted ORs for MI in smokers was 3.65 (CI 2.67-4.99) and for snus users 0.96 (CI 0.65-1.41) compared to nonusers. After adjustment for CV riskfactors the OR were for smokers 3.53 (CI 2.48-5.03) and for snus users 0.58 (CI 0.35-0.94).

Bolinder (10) surveyed 135.036 construction workers during the 1970 of whom 6 297 were snus users. Mortality was observed during a 12 year period during which 220 snus users died of CV disease. Relative risk for smokers of more than 15 cigarettes per day was 1.9 (1.7-2.2) and for snus users 1.4 (1.2-1.6). The increased risk in snus users occurred mainly in old age. Tobacco consumption habits were noted only in the beginning of the study and it is possible that snus users may have also smoked during the 12 year study period. Snus use was less common during the 1970 and the characteristics of today's users may differ.

The conclusion from these studies as from the nicotine replacement studies is that there is certainly a significant difference in the effects of smoking and snus on the likelihood to develop a CV disease.

Snus and its Association with Oral Cancer

Snus use has clearly observable effects on the oral mucosa to which it is compressed, between the upper lip and the gum. The mucosa on the gum often undergoes a leukoplakia like process. It has therefore been natural to suspect that snus can cause oral cancer, which actually seem to be

the case with many of the smokeless products. Three relatively recent studies have addressed this question with snus.

First Lewin (11) in a case referent study with 605 cases and 756 controls on head and neck cancer found no increased risk for snus users compared with non tobacco users. Current smokers had a relative risk of 8.4 while the snus users had a relative risk of 1.0.

Schildt (12) performed another case referent study with 410 patients with oral cancer and 410 controls. Active snus use had an OR of 0.7 (CI 0.4-1.1) while smokers had an increased risk, OR 1.8, (CI 1.1-2.7).

More recently Nyren (personal communication) found no association between oral cancer and snus use.

The conclusion from these three studies seem to be that the Swedish snus, for some unknown reason, is not associated with oral cancer as other similar products can be. Moreover the Swedish oral cancer incidence is one of the lowest in Europe even though snus is only widely used use in Sweden.

Nicotine Use in Sweden and Tobacco Related Harm

In 1980 36% of the Swedish men smoked and 15% used snus. In 1999 the figures were 17% for smoking and 19% for snus. These are daily use figures with relatively little overlap between smoking and snus use. This indicates that around 35% of Swedish men are using nicotine. Also nicotine replacement products have a large penetration in Sweden, actually the largest in the world except for Island. I have estimated that of the nicotine consumed in Sweden, about 2/3 originates from smoked products and 1/3 or a little more from the non smoke products, mostly snus and a few percent nicotine replacement products. It is interesting to see that in Petos (13) estimation of tobacco related mortality, Swedish men are in the bottom, i.e. have the lowest risk in the developed countries. This is despite the fact that total nicotine use among Swedish males doesn't seem to be any less than in most other European countries. Specifically lung cancer risk differs significantly between men in Sweden and neighbouring countries, Denmark and Norway despite similarities in origin, environment and culture.

Nicotine Replacement Induced Reduced Smoking and Harm

During the last years several controlled studies to aid reduced smoking and harm have been performed, see review by Fagerström (14). These studies show that reduced smoking can be aided by nicotine replacement and that active product mostly have been found to be better than placebo. The long term magnitude of the effects are not impressive particularly when indicators of toxic intake are assessed. When fewer cigarettes are smoked the remaining cigarettes are usually smoked more effective. Since the above review was written 1) active nicotine gum has been found to aid reduced smoking better than placebo (Jimenez-Ruiz personal communication) 2) use of the nicotine inhaler (on the US market) resulted in harm reduction i.e. improved cardiovascular risk factor profile 4 months into the study (Bolinger) and 3) Eclipse and use of the nicotine inhaler both quite significantly reduce smoking although COHb increased when Eclipse was used, and a reduction well over 50%, can be maintained over long time (8 weeks) in smokers that could choose what product they wanted to use (15).

As has been pointed out by others e.g. Warner (16) the current nicotine replacement products are not good enough in delivering nicotine in terms of absolute dose and speed of delivery. However if a true nicotine inhaler were devised (the current "inhaler" does not deliver nicotine to the lungs) a nicotine – only OTC product might be readily acceptable to smokers.

Concluding Remarks

If smokers smoke largely for obtaining nicotine there seem to be a compelling case for harm reduction. The safety of pure nicotine is no doubt much better than when obtained from products that no doubt set tobacco on fire. The only real problem could be if the neurotoxic effects of nicotine as seen in rats would apply to humans. However the problem with nicotine in this special and isolated situation should not hinder us from harvesting the large health gains to be obtained from reducing tobacco smoking in general.

Tobacco can be more or less harmful. One direction of development can be to modify tobacco products as has been done with the Swedish snus. The other route, and possibly even less harmful, is to offer tobacco smokers pure nicotine products that are more effective, available, cheaper and in a larger selection to suit more smokers.

Idea for a Study

In order to test some of the new ideas around harm reduction I would like to see a study that used two separate populations e.g. companies, towns as has been done in several tobacco control studies (e.g. COMMIT).

In one of the populations (A) the prevailing message and communication of quitting and quitting abruptly should be delivered.

In the other population (B) various options in terms of procedures and goals should be given such as quitting abruptly, quitting by gradual reduction, reducing smoking and switching to safer products. Various tools that could aid reduced harm such as nicotine replacement products and possibly smokeless products as Swedish snus together with behavioural procedures should be offered liberally.

The evaluation would take place over many years and include a multitude of measures such as e.g. complete quitting from smoking, amount smoked, quality of life, indicators of harm reduction such as CO in expired air, measures of tobacco toxins CV risk factors, health status and motivational and attitudinal factors to smoking.

If B turned out to be better a dismantling strategy needs to follow.

Further contact: If the Institute of Medicine would like to discuss these matters further I would be happy to be of assistance.